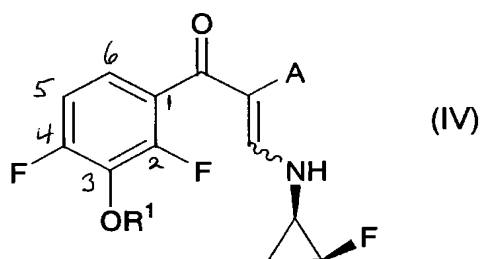


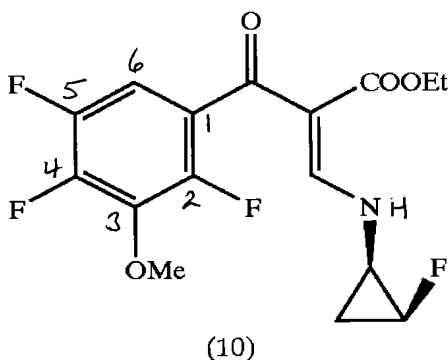
REMARKS

Applicants thank the Office for withdrawing the rejections of the original claims as anticipated by Takemura '225 (U.S. Patent No. 6,900,225) and Takemura '757 (U.S. Patent No. 5,849,757) as set forth in the March 10, 2009 Office Action.

The Office now rejects the claims as obvious over the Takemura '225 and Takemura '757 patents. The Office takes the position that the ring closure step of the presently claimed process is obvious in view of the ring closure step of the Takemura '225 and Takemura '757 processes.

Applicants pointed out in the Amendment filed in the present application on September 8, 2009, that the processes of the Takemura '225 and Takemura '757 patents are different from the processes of the present claims for the reason, *inter alia*, that the Takemura processes are carried out on different chemical compounds. One difference in the processes of the present claims and the processes of Takemura is reflected in the structure of compound (IV) of present Claim 1 in comparison to the quinoline-type compounds of the Takemura patents. For convenience Applicants reproduce below compound IV recited in present Claim 1 and a quinoline-type intermediate of the Takemura '225 process (i.e., compound (10) in column 8 of Takemura '225).



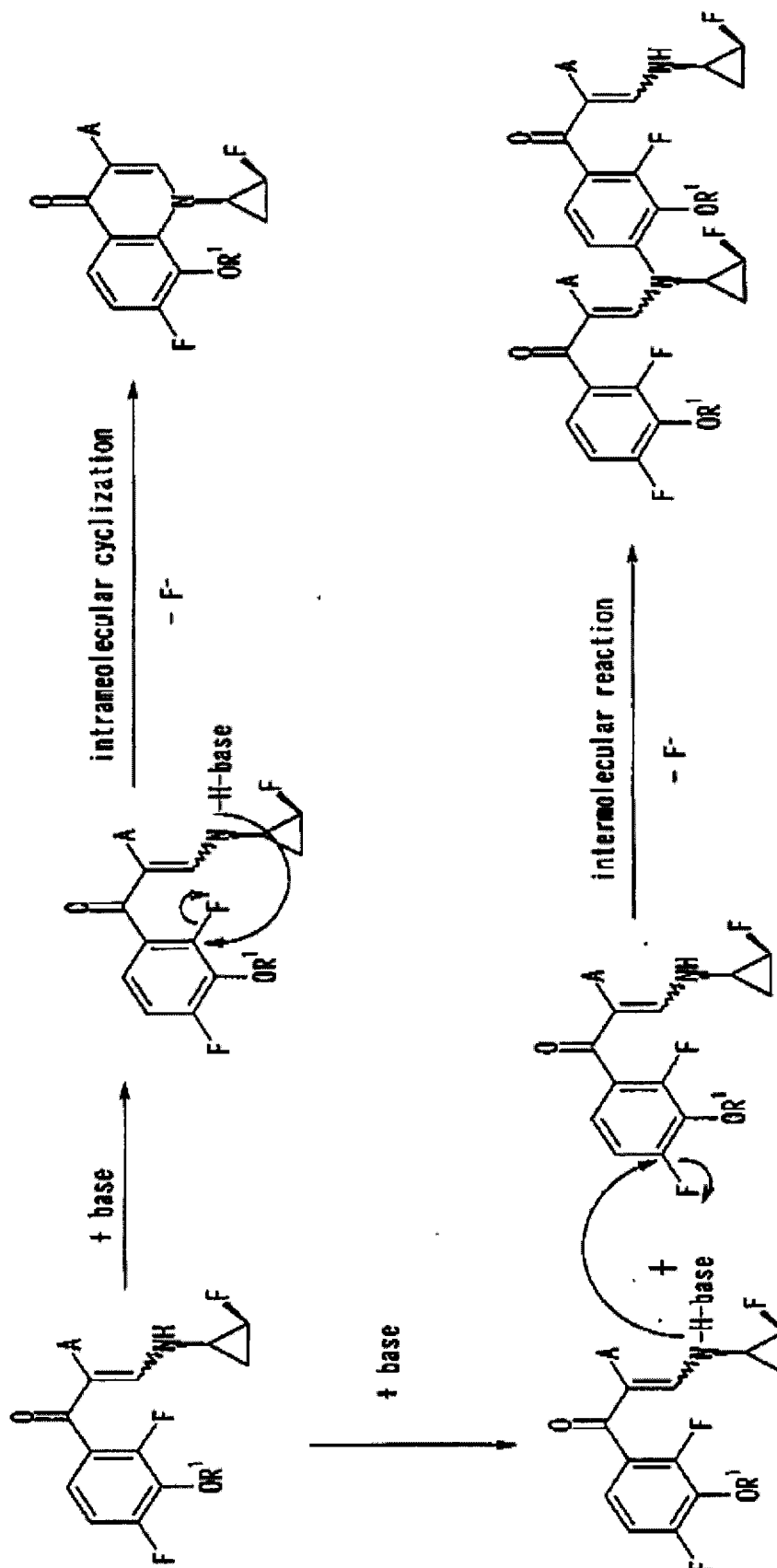


It is readily evident that one of the differences between present compound (IV) and the intermediate compound (10) of Takemura '225 lies in the benzene ring core of the respective compounds. Compound (IV) is substituted by only two F atoms in 2 and 4 positions. Compound (10) of Takemura '225 includes a benzene core that is substituted with three F atoms that are in 2, 4 and 5 positions.

In the reaction mechanism under which each of the compounds of formulas (IV) and (10) undergo reaction in the presence of a base, the base acts on the amino group of the fluorocyclopropyl moiety so that the lone pair of the nitrogen atom is activated. Such an activated lone pair undergoes a nucleophilic substitution reaction by acting on carbon atoms. As a result, this reaction takes place either on an 2-position carbon atom or on a 4-position carbon atom at the site affected by the reaction. When the 2-position carbon atom is attacked, an intra-molecular reaction takes place and results in a ring closure reaction of a quinolone ring. Meanwhile, the reaction that occurs at the 4-position carbon atom is an inter-molecular reaction which forms a substituted compound. The reaction mechanisms for these reactions is shown below.

In the case of an intra-molecular ring closure reaction, there seems to be no substantial difference in the structure surrounding the reaction site of each of the compounds of formulas (IV) and (10). However, the compound of formula (IV) is less reactive perhaps because this compound lacks one fluorine atom.

In the case of an inter-molecular reaction, which occurs at position 4, what matters is the steric environment around the position 4, namely the effect of the substituents on the two carbon atoms adjacent to the position 4 carbon atom. The compound of formula (10) has a third fluorine atom on the benzene core and is thus further activated in comparison with compound (IV) which does not have a third fluorine atom. However, on the other hand, the third fluorine atom is located at the adjacent carbon atom and this makes the reaction site more hindered than compound (IV). The compound (IV) is more open to proceed an inter-molecular reaction at position 4, because this has the substituent on only one of the adjacent two carbon atoms. From the viewpoint of the steric hindrance around position 4, more steric hindrance is observed in compound (10) and perhaps making the inter-molecular reaction less advantageous in the case of compound (10) than compound (IV).



Compound (10) of Takemura '225 is further fluorine substituted at a 5 position of an aromatic ring thus reinforcing a higher degree of nucleophilic reactivity in comparison to compound (IV) of the present claims. Such higher nucleophilic reactivity would not be seen as an advantage with respect to any nucleophilic ring-closure reactions carried out on the Takemura '225 compound (10). While compound (10) of Takemura '225 may undergo intra-molecular aromatic nucleophilic substitution there is no basis that a similar reaction would be expected to take place for the compounds recited in the present claims.

Moreover, compound (10) of Takemura '225 is substituted at a 3 position by an alkoxy (OR¹) group. The corresponding 4 position of compound (IV) of the present claims, in contrast to the doubly substituted compound (10) of Takemura '225, has only a single substituent on two adjacent carbon atoms. The 4 position of compound (IV) may therefore be advantageous with respect to inter-molecular nucleophilic substitution in contrast to intra-molecular nucleophilic substitution at a 2 position.

Further still, with respect to intra-molecular ring formation, it is known that the formation of a six-membered ring is not always favored over the formation of a five-membered ring which may further make advantageous the inter-molecular substitution reaction in comparison to the intra-molecular ring closure reaction. While intra-molecular cyclization reactions are known, in many cases such reactions are carried out advantageously under particular conditions such as in dilute solutions of inert solvents. The presently claimed invention requires no such particular conditions.

The process of the present claims, in comparison to the process of the cited references, permits successful intra-molecular nucleophilic substitution at a 2 position of an aromatic ring. For example, compound (10) has three F atoms at 2, 4 and 5 positions of the benzene ring, respectively. The F atom at the 4 position activates compound (10) even if the

nucleophilicity of the fluorinated cyclopropyl amine is weakened. Thus, nucleophilic substitution of compound (10) proceeds more advantageously as far as the reaction at the 2 position is concerned in comparison to compound (IV). The claimed method is thus substantially superior and unexpectedly excellent in comparison to the processes and disclosure of the cited references.

Applicants thus submit that the Office assertion that it would be obvious to subject the compound of formula (IV) of the present claims to the same reaction step described in the Takemura '225 or Takemura '757 patents is not supportable as a matter of fact and further that those of ordinary skill in the art would not have a reasonable expectation of forming the same or similar ring closure products using a compound having a different pattern of aromatic substitution in comparison to Takemura.

For the reasons discussed above, Applicants request withdrawal of the rejection and the allowance of all now-pending claims.

Respectfully submitted,

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